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HARNESS, DICKEY & PIERCE, P.L.C.
P.O. BOX 8910
RESTON, VA 20195

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,508	GUSTAVSSON ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-23* is/are rejected.

7)☒ Claim(s) *10 and 19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 11/12/2009, are acknowledged and entered. Claims 1-7 have been cancelled by Applicant. Claims 8-23 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 1-7 are withdrawn as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments, filed 11/12/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Drawings

The drawings were received on 11/12/2009. These drawings are accepted by the Examiner.

Claim Objections

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 depends from claim 8 and recites the limitation: "...wherein said multi-targeting antifolate is selected from the group consisting of pemetrexed, ralitrexed, and lometrexol". Claim 8 recites that the multi-targeting antifolate is selected from pemetrexed, ralitrexed, and lometrexol. Claim 10 thus does not further limit claim 8 from which it depends.

Claim 19 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 19 depends from claim 17 and recites the limitation: "...wherein said multi-targeting antifolate is selected from the group consisting of pemetrexed, ralitrexed, and lometrexol". Claim 17 recites that the multi-targeting antifolate is selected from pemetrexed, ralitrexed, and lometrexol. Claim 19 thus does not further limit claim 17 from which it depends.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 91/17660** (Published November 28, 1991) in view of **Hanauske *et al.*** (The Oncologist, 2001, vol. 6, pages 363-373) and **Niyikiza *et al.*** (Molecular Cancer Therapeutics, May 2002, vol. 1, pages 545-552).

The instant claims are drawn to compositions and kits comprising at least one of tetrahydrofolate, methylene-tetrahydrofolate and methyl-tetrahydrofolate, and at least one multi-targeting antifolate, optionally in further combination with at least one

chemotherapeutic agent as well as methods of treating cancer comprising administration of at least one of tetrahydrofolate, methylene-tetrahydrofolate and methyl-tetrahydrofolate, and at least one multi-targeting antifolate, optionally in further combination with at least one chemotherapeutic agent.

WO '660 teaches 5,10-methylene-tetrahydrofolate (CH_2FH_4) and its solution isomer FH_4 (tetrahydrofolate) as modulators of the *in vivo* antitumor effects of the antifolate 5-fluorouracil (Abstract; page 1, lines 5-13). The therapeutic mechanism of 5-fluorouracil against colon cancer cells is disclosed to be complete inhibition of thymidylate synthase (TS) or abrogation of TS activity (page 1, lines 23-29). CH_2FH_4 (*i.e.*, methylene-tetrahydrofolate) is a normal intracellular metabolite of the B-vitamin, folic acid, for use in thymidylate synthesis by TS (page 4, lines 23-25). The inventors disclose compositions and methods comprising CH_2FH_4 or FH_4 and 5-fluorouracil for the treatment of cancer (page 10, lines 8-17). The CH_2FH_4 or FH_4 may be administered concurrently with 5-fluorouracil or prior to the administration of 5-fluorouracil as recited in claims 21 and 22 (page 10, lines 12-14). The CH_2FH_4 or FH_4 can be administered as the biologically active isomers as recited in claims 2, 9, 15, and 18 (page 11, lines 6-8; page 18, lines 6-16). WO '660 discloses that CH_2FH_4 of FH_4 can be used in a method to reduce the toxicity of "an anti-folate drug" which has been administered to a patient. Examples of such anti-folate drugs include methotrexate, trimetrexate, nitrous oxide, and dideoxytetrahydrofolic acid (page 11, lines 14-19; page 19, lines 7-22). Combination chemotherapy with additional chemotherapeutic agents as recited in claims 4, 11, 16, and 20 is disclosed at page 18, lines 17-33).

The instant claims differ from the disclosure of WO '660 in that the primary reference does not explicitly disclose combining methylene-tetrahydrofolate or tetrahydrofolate with a "multi-targeting antifolate" such as pemetrexed.

However, Hanauske *et al.* teach that pemetrexed is a novel antifolate clinically active against multiple solid tumors, including non-small cell lung cancer, breast, mesothelioma, colorectal, pancreatic, gastric, bladder, cervix, and head and neck (Abstract; pages 366-369; Table 3). Pemetrexed is a multi-targeting antifolate that inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide

ribonucleotide formyltransferase (GARFT), and aminoimidazole carboxamide ribonucleotide formyltransferase (AIRCARFT) (Abstract; page 363, right column to page 364, left column; Figure 2). As taught in Hanauske *et al.*, it was known in the art that folic acid added to the diet in preclinical studies reduced the toxicities of pemetrexed while maintaining antitumor activity (Abstract). The authors further disclose that combining pemetrexed with other antitumor agents (*e.g.*, 5-fluorouracil or paclitaxel) results in a synergistic effect (page 365, left column). Similar additive or synergistic effects were obtained when pemetrexed was combined with gemcitabine, carboplatin, cisplatin, oxaliplatin, cyclophosphamide, or doxorubicin (page 365, left column). Also see pages 369 to 370 and Table 4. Preliminary studies have indicated that addition of folic acid ameliorates toxicities permitting dose escalation of pemetrexed (page 371, left column).

The primary and secondary references discussed above thus teach that CH_2FH_4 or FH_4 are useful in combination with 5-fluorouracil and other anti-folate drugs, that the multi-targeting antifolate pemetrexed was known in the art to be effective against multiple cancer types, both alone and in combination with other chemotherapeutic agents, and that addition of folic acid ameliorates toxicities of pemetrexed.

Niyikiza *et al.* is provided as further motivation to administer tetrahydrofolate, methylene-tetrahydrofolate, and/or methyl-tetrahydrofolate in combination with the multi-targeting antifolate pemetrexed. In this regard, Niyikiza *et al.* teach that high pretreatment levels of homocysteine and/or methylmalonic acid are predictive of severe toxicity associated with pemetrexed therapy (Abstract; pages 547-549; Figure 3). Based on this observed correlation, the authors suggest that by reducing homocysteine and/or methylmalonic acid levels (*e.g.*, by administration of folic acid), one could substantially reduce a patient's risk for severe toxicity while maintaining efficacy of the drug. The authors thus disclose a study of supplementation with folic acid and vitamin B_{12} for all patients participating in pemetrexed clinical trials. Such supplementation reduces homocysteine and, in turn, results in significant reduction of toxicity associated with pemetrexed therapy, while maintaining, or possibly improving, efficacy (page 551, right column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate compositions and kits comprising tetrahydrofolate, methylene-tetrahydrofolate, and/or methyl-tetrahydrofolate and pemetrexed and administer such a combination to a patient with cancer. The skilled artisan would have been motivated to do so because tetrahydrofolate, methylene-tetrahydrofolate, and methyl-tetrahydrofolate are known biologically active metabolites of folic acid (see WO '660; Figure 2 of Hanauske *et al.*; and Figure 1 of Niyikiza *et al.*). Because pemetrexed inhibits multiple enzymes responsible for conversion of folic acid to these compounds, and for the conversion of these compounds to one another, the skilled artisan would expect that administration of one or more of these compounds in combination with the multi-targeting antifolate pemetrexed would allow these compounds to elicit their biological activity without having to first be formed *in vivo* from folic acid or one another. Such is evidenced by WO '660, who teach administration of methylene-tetrahydrofolate or tetrahydrofolate rather than folic acid *per se* in combination with antifolate compounds. The skilled artisan would expect that if the methods disclosed in WO '660 are effective with antifolate compounds that target one enzyme, then they would also be effective with antifolate compounds that target multiple enzymes. This is especially true because pemetrexed inhibits the same enzyme (TS) as 5-fluorouracil. Furthermore, because methyl-tetrahydrofolate is involved in the conversion of homocysteine to methionine (see Figure 1 of Niyikiza *et al.*), the skilled artisan would expect that administration of methyl-tetrahydrofolate would be effective in reducing homocysteine levels in patients undergoing pemetrexed therapy, which would be reasonably expected to reduce pemetrexed toxicity as discussed in Niyikiza *et al.*

With regard to claims 5 and 12, it would have been obvious to one of ordinary skill in the art that if the methylene-tetrahydroformate, methyl-tetrahydrofolate, and/or tetrahydrofolate are administered prior to or after the antifolate, that they would be formulated in different pharmaceutical compositions. Similarly, if the methylene-tetrahydroformate, methyl-tetrahydrofolate, and/or tetrahydrofolate are administered simultaneously with the antifolate, then they would be formulated in the same composition as recited in claims 6 and 13.

With regard to claims 14-16, kits comprising pharmaceutical agents are commonplace in the art. The skilled artisan would immediately recognize the benefit of providing pharmaceutical compositions in kits for ease of storage, transport, and administration to patients.

Response to Arguments

Applicant's arguments filed 11/12/2009 have been fully considered but they are not persuasive. Applicants attach Figures 1-6 illustrating a comparison, in terms of efficacy and toxicity in alleviating the symptoms of cancer when using a combination of pemetrexed and methylene-tetrahydrofolate (as claimed in one embodiment of the invention) and a combination of pemetrexed and folic as taught in the cited prior art. The Examiner is not persuaded that Applicants have that "combining at least one of tetrahydrofolate, methylene-tetrahydrofolate, and methyl-tetrahydrofolate, and at least one multi-targeting antifolate selected from the group consisting of pemetrexed, raltitrexed and lometrexol" achieves "unexpected results relative to the compositions as taught by Hanauske and Niyikiza" as asserted by Applicants.

As a first matter, Applicants state that folic acid intake was "about 500 μg/day, which is a level normally employed when using folic acid with the aim of reducing toxicity" (citing Niyikiza, page 551, left column, penultimate paragraph). Niyikiza states at page 551, left column, penultimate paragraph, "Beginning March 2000, supplementation throughout the study with daily folic acid (350 -1000 μg) and vitamin B12 (1000 μg i.m. every 9 weeks) was established for all patients participating in pemetrexed clinical trials". The doses of folic acid disclosed in Niyikiza are for human patients, not rats as utilized in Applicant's examples.

Secondly, 500 μg/day folic acid administered to the rats in Applicant's examples is approximately 2.5 mg/kg. This value is based on the weight of the rats being 200 g (*i.e.*, 0.2 kg). As discussed in the cited prior art, methylene-tetrahydrofolate is a normal intracellular metabolite of folic acid. As such, folic acid is naturally metabolized to methylene-tetrahydrofolate *in vivo*. However, the dose of methylene-tetrahydrofolate administered to the rats in Applicant's examples was 15 mg/kg, over 7x the dose of folic acid administered. Clearly, administration of 0.2 mg/kg folic acid will result in less than

0.2 mg/kg of the metabolite methylene-tetrahydrofolate *in vivo*. Accordingly, it is the position of the Examiner that Applicants did not administer a sufficient dose of folic acid to produce a sufficient amounts of tetrahydrofolate, methylene-tetrahydrofolate, and/or methyl-tetrahydrofolate *in vivo* to have an effect in reducing the toxicity of pemetrexed and/or increasing the efficacy of pemetrexed as suggested and motivated by the cited prior art.

Thirdly, Applicant's examples as limited to a specific dose of methylene-tetrahydrofolate (15 mg/kg) combined with either 1.0 mg/kg or 2.0 mg/kg of a single multi-targeting antifolate (pemetrexed) for the treatment of a single type of tumor (adenocarcinoma). The showing in the recited examples are not commensurate in scope with the claimed invention, which encompasses combinations of tetrahydrofolate, methylene-tetrahydrofolate, and/or methyl-tetrahydrofolate and pemetrexed, ralitrexed, and/or lometrexol in any amounts for the treatment of any cancer.

Accordingly, the Examiner is not persuaded that Applicants have demonstrated an unexpected result commensurate in scope with the claims. It is not *per se* unexpected for one therapeutic to be more effective than another. Applicant's showing that 15 mg/kg methylene-tetrahydrofolate is more effective than 500 mg/day folic acid in increasing the efficacy and reducing the toxicity of 1.0 or 2.0 mg/kg pemetrexed is not persuasive of an "unexpected result" as asserted by Applicants. As discussed supra, it was known in the art that tetrahydrofolate, methylene-tetrahydrofolate, and methyl-tetrahydrofolate are metabolites of folic acid in vivo and that folic acid increases the efficacy and reduces the toxicity of anti-folate drugs. As such, the expectation is that tetrahydrofolate, methylene-tetrahydrofolate, and/or methyl-tetrahydrofolate will also be effective in reducing the toxicity of and/or increasing the effectiveness of anti-folate drugs as suggested and motivated by the teachings of the cited prior art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

January 29, 2010